Metabolism 12: Glycogen Storage Diseases

Introduction

Most texts will tabulate these as six different diseases, as if putting them in a table aids their memorization. It doesn't. Instead, we're going to **derive the symptoms**. We first need to decide **which cell it happens in** (muscle, liver, or both), then look at **glycogen accumulation** or lack thereof: if there's a problem with making it (will not accumulate) or a problem with breaking it down (will accumulate). Finding out those two things will get us far. We'll use this lesson to review glycogen metabolism and also provide some clues and memory aides to get these questions right come test day.

Memory Techniques

Type 1 and type 6 (the edges of the table) are **hepatic cells only**.

Type 5 is the **only muscle-only** disease, and it's called McArdle (for muscle).

Types 5 and 3 can live past 2 years (and "2" is the difference between them), and type 5, being muscle-only, isn't fatal.

The others are **both hepatocytes and myocytes**.

Hepatic cells are supposed **to make glucose for other cells**, so failure will result in hypoglycemia.

Muscle cells are supposed to **use glycogen to keep going**, so failure will result in weakness and muscle breakdown.

Accumulation is bad, causes inflammation, and leads to scarring of whatever organ happens to be accumulating glycogen.

The Table

TYPE	EPONYM	ORGAN	ENZYME	ACCUMULATION	GLYCOGEN	SYMPTOMS
I	Von-Gierke	Hepatic	Glucose-6-phosphatase	Yes	Normal	Huge liver, intellectual disability, doll's face, short limbs
II	Pompe	Both	Lysosomal 1,4 glucosidase	Vesicular inclusion	Normal	Hypoglycemia, hypotonia, death by 2
III	Cori	Both	Debranching enzyme	Mild	Many short branches	Mild hypoglycemia, mild hypotonia
IV	Anderson	Both	Branching enzyme	No	Long chains without branches	Hypotonia, cirrhosis, death
V	McArdles	Muscle	Glycogen phosphorylase	Yes	Normal	Cramps, weakness, myoglobin, 20 yrs old
VI	Hers	Hepatic	Glycogen phosphorylase	Yes	Normal	Hypoglycemia, cirrhosis, death by 2

Table 12.1

We've opted to follow the order of the physiology and memory cues rather than the order of the table. The test won't ask, "what type # is this." The test will ask, "what is the enzymatic deficiency" or "what does the glycogen look like," so doing them in order, to keep the numbers chronological, won't help on test day.

Type I is "1 or 6" so we know that it's a disease of the liver. It makes sense, since it's a deficiency of **glucose-6-phosphatase**. Only the liver has glucose-6-phosphatase, the enzyme that releases glucose from the hepatocyte back into circulation. No other cell has that, because no other cell makes glucose for everyone else. Well, without glucose-6-phosphatase, anything the liver does to preserve blood glucose fails. Glycogen works normally, depositing and withdrawing. Even gluconeogenesis works. **But nothing can get out of the liver**. If the body relies on the liver to maintain blood glucose, and it can't get glucose out of the hepatocytes, then there will be **severe hypoglycemia**. And because all of this glucose is stuck in the liver, the liver is going to get big, presenting as a **protruding abdomen**. But it isn't glycogen, so there's no scarring, no cirrhosis. In a developing baby with Type I, glucose to transport (to everywhere) is inhibited, and so brain development slows **(doll-like-face)**, they don't grow **(short stature)**, and they have **emaciated extremities**, especially relative to the big abdomen. And the **biggest thing is that glucose-6-phosphatase** isn't just the end of glycogen liberation. It is also the end of gluconeogenesis. The fasting hypoglycemia is the most severe of all the diseases of this type.

Type VI is the other "1 or 6" disease. Type VI is called "Hers" disease, reminding us that it's the "Hepatic" version of **glycogen phosphorylase** deficiency. The **storage half** of glycogen works perfectly, so when looking at the glycogen under a scope the **glycogen looks normal** (branches and straight chains). The problem with this disorder is that glycogen, once stored, can never be extracted, never come out of storage. Since glycogen is the temporizing maneuver between insulin-glucose and glucose-from-gluconeogenesis, and these people (babies) can't use glycogen, there'll be **hypoglycemia**. It's not as severe as Type I, because gluconeogenesis still works. But the accumulation is the problem. Glycogen stores **accumulate**, so the liver gets big. **Accumulation of glycogen** leads to **cirrhosis** early in life, with death by age 2.

Type V is the **only muscle-only** disorder, called McArdle disease, and is the "Muscle" form of **glycogen phosphorylase** deficiency. Type VI and Type V are both deficient in glycogen phosphorylase. Type VI is hepatic-only; Type V is muscle-only. Because the liver works, there's no hypoglycemia or cirrhosis. The liver gets glucose to all the cells that need it. It's in the muscle that there's a problem. Muscles use glycogen only when they need to — when the muscles are being used more than normal. Sitting at a desk studying for an exam doesn't burn glycogen, whereas jogging around the block will require glycogen to keep the legs supplied with glucose. These patients (youth) **can't mobilize muscle glycogen**, so suffer the consequences whenever **they use their muscles**. This presents with **muscle cramps**, **weakness**, and if they push themselves at all, florid **myoglobinuria** from muscle breakdown. Even with excellent perfusion, glucose, and oxygen, our muscles depend on glycogen to push through the use. Without access to glycogen, muscles just don't work; they die as if they were hypoxemic. These patients **live**, and present with **exercise intolerance**, usually pain in the muscles on any exertion. It most commonly presents in the **teens and twenties**.

The remaining disorders affect both hepatic cells and muscle cells. Types III and IV are within the pathway we know. Type three is **debranching enzyme deficiency**, and Type IV is branching (the other one).

Type III, Cori disease, is a problem with the **debranching enzyme**. This means that glycogen phosphorylase can chew down those long strands without problem. And since nothing is wrong with glycogen synthesis, glycogen is stored and some of it is used. Because some glycogen can be used, muscles can do more than in Type V, so it's not as severe. Because the liver can use glycogen a little, and it performs gluconeogenesis, there's only a mild hypoglycemia. So **mild hypoglycemia** and **mild**

weakness/cramping are present. But because glycogen can't be cleared past the branch, **glycogen will accumulate**. The resulting inflammation and scarring won't be as severe as a glycogen phosphorylase deficiency (V and VI), so there will be **hepatomegaly without cirrhosis**. On a biopsy, glycogen will show many, many branches, all with short little nubs, sometimes even with **only one glucose** on the outermost branch.

Type IV, Anderson disease, is a problem with **branching enzyme**. Branching enzyme deficiency means that **glycogen can't branch**. Glycogen synthase can keep adding lengths and glycogen phosphorylase can chop them down. But without branches, the density of the stored glucose is small, so it's as if there were no glycogen. This presents with **hypotonia** (a mild form of the severe weakness seen in Type V). This one breaks the mold. Even though chains can be built and taken down, just not branched (which means there shouldn't be an accumulation), there's **cirrhosis anyway** and **death by age 2**. By the logic of physiology, this seems like it shouldn't be that bad, but it is.

Finally, **Type II**, Pompe disease. We saved it for last as we haven't discussed its physiology yet. When there's too much glycogen stored in a cell, **lysosomes** come to degrade it. The problem with Pompe disease is that the **lysosomes envelop the chains**, **no problem**, but lack the ability to **degrade the chains within the lysosome**. There's a deficiency of **lysosomal-1,4-glucosidase**. "Too much glycogen" happens all the time. Muscles have a little more room than the heart does, but these muscles are designed to care only so much. The lysosomes are supposed to keep it in balance. But now the **lysosomes accumulate**, unable to clear their contents. They accumulate as **vacuoles (inclusion bodies)** in the muscles and, in particular, the **heart**. This causes osmotic shifts and **cardiomegaly**. The inclusion bodies slowly scar, leading to **weakness** and **heart failure**. The glycogen looks normal but there are inclusion bodies. These patients **die within 2 years**.